REMARKS

Claims 1-24, as amended, and new claims 40-54 appear in this application for the Examiner's active consideration.

The specification has been amended to include the continuity data with regard to PCT/IL2004/000881 filed September 22, 2004, which further claims priority from provisional application 60/503,902 filed September 22, 2003. This change is supported by Applicants' PCT application of which this application is a national stage filing. It also is similar to the change requested by way of a preliminary amendment filed March 21, 2006 which apparently was not entered.

Claim 1 has been amended to emphasize that the API solution produced from the method of the invention is stable, support for which is found through the application, e.g., paragraphs [0022] and [0024] of the published application. Claims 25-39 have been canceled and are now rewritten as dependent process claims 40-54 which should be examined as they are process claims according to the Group I classification. The new claims are supported by the specification and canceled claims 25-39 so that there is no issue of new matter.

Accordingly, as no new matter is introduced by the specification and claim amendments, they all should be entered at this time.

Specification

The specification has been objected to for failure to contain the continuity data with regard to PCT/IL2004/000881 filed September 22, 2004, which further claims priority from provisional application 60/503,902. In response, as noted above, the specification has been amended to include such information.

Claim Rejections - 35 USC § 103

Claims 1-24 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over US Patent No. 6,462,180 to Lebing et al. (referred to hereinafter as "the '180 Patent") further in view of US Patent No. 5,610,285 to Lebing et al. (referred to hereinafter as "the '285 Patent").

Applicants traverse this rejection.

The Office Action includes a summary of the purification processes disclosed in the '180 Patent and in the '285 Patent. In brief, the '180 Patent discloses two chromatography steps: a first step employing an anion exchange resin, and a second step in which the eluted solution obtained from the anion exchange resin is passed through a cation exchange resin (see, e.g., col. 3, ll. 31-33 of the '180 Patent). The '285 Patent discloses at least one cation exchange chromatography; preferred embodiments describe a first chromatography step employing anion exchange resin followed by two cation exchange chromatography steps (see, e.g., Fig. 2 and col. 3, ll. 18-19 of the '285 Patent). The Examiner acknowledges that both the '180 and the '285 Patents do not teach a step wherein the eluent from the cation exchange step is submitted to an anion exchange step, as presently claimed. However, the Examiner alleges that "...selection of any order of performing steps is *prima facie* obvious in the absence of new or unexpected results." Applicant respectfully disagree.

First of all, it is well known in the field of protein purification that the order of performing steps is of significant impact on the characteristics of the product obtained. For example, the '285 Patent discloses as a preferred embodiment performing the viral inactivation step before loading the second cation exchange chromatography (see, e.g., Fig. 2 of the '285 Patent). The '180 Patent discloses that viruses are deactivated prior to dilution of the purified solution and its addition to an anion exchange resin (see, e.g., col. 3, ll. 19-21 of the '180 Patent).

Moreover, it should be noted that unlike the cited art, the process of the present invention can effectively be carried out on a commercial scale, and results in an API solution which is not only highly pure and active, but is also stable and ready to use as a pharmaceutical formulation containing the purified API.

Furthermore, the ready-to-use solution of the present invention is stable, without the need for stabilizer, and yet stability is maintained for at least 3 months and up to 36 months (see, e.g., paragraphs [0024] and [0053]-[0055] of the published application). The cited references do not disclose a process that can produce a purified API that is highly stable, such that the end product can be a solution devoid of stabilizers. In contrast, the '285 Patent particularly discloses that stabilizers are added when the lyophilizate containing API is dissolved in water (see, e.g., col. 5, l. 65 to col. 6, l. 1 of the '285 Patent) while the '180 Patent specifically states that the resulting solution is lyophilized (see, e.g., col. 8, ll. 34-35 of the '180 Patent). There are unexpected advantages of the inventive process which results in an API that can be directly used in an

aqueous solution devoid of any stabilizer. Because of the high stability, there is no need to lyophilize the solution for storage and then to re-dissolve the powder before use, which is time consuming and may introduce impurities to the reinstated solution (see, e.g., paragraph [0122] of the published application). In addition, the pure API preparation of the present invention can be administered to any subject in need thereof, without the concern of side effects resulting from the added stabilizers. For example, there is no restriction of diabetic subjects from receiving the API composition of the present invention, which does not comprises sucrose as stabilizer (see, e.g., paragraph [0112] of the published application). In contrast, the diabetic subjects cannot receive the API composition of the '285 Patent which contains sucrose as a stabilizer.

Finally, the process of the present invention is further distinguished from those processes disclosed in the cited references in the use of one type of buffer throughout the process steps. The use of one type of buffer simplifies the process and makes it suitable for a large-scale production (processing of source material in the range of tens of kilograms). The '180 Patent states that the process disclosed in the '285 Patent is too resource intensive for large-scale manufacturing (see, e.g., col. 2, ll. 49-50 of the '180 Patent), but fails to disclose any quantities itself. In contrast, the instant specification provides examples of actual large scale production, employing, e.g., anion exchange chromatography column of 316 liters (see, e.g., Example 2 and paragraph [0144] of the published application) and API containing solutions of ten of kilograms (concentrated effluent of 100 kg, see, e.g., Example 3 and paragraph [0152] of the published application).

Thus, the present invention provides a novel process for large scale production of API, which results in an unexpectedly pure, unexpectedly stable product suitable for use in an aqueous ready-to-use solution without the need for addition of protein stabilizers or lyophilization as in the art. Therefore, the rejection over the '180 Patent in view of the '285 patent should be withdrawn.

In view of the foregoing, it is respectfully submitted that the entire application is now believed to be in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of this application.

Respectfully submitted,

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